COPY

September 29, 1958

Duane G. Wenzel, Ph.D.
Professor of Pharmacology
The School of Pharmacy
University of Kansas
Lawrence, Kansas

Dear Dr. Wenzel:

We recently ran across your May 1958 article in the Journal of the American Pharmaceutical Association on the Effect of Nicotine on Experimental Hypercholesterolemia in the Rabbit. This was read with considerable interest.

I would assume that this represents the preliminary work you had carried out in this field before receiving the grant from Tobacco Industry Research Committee since it does not contain any acknowledgment to the Committee. It does nevertheless have a very close bearing upon the present project and I think that all members of the Scientific Advisory Board will be glad to have a copy of it along with the copy of your recent progress report which is about to be distributed. Can you supply me with two dozen reprints? We will be glad to defray the cost. We will also want two dozen reprints of any future papers resulting from the project or relating closely to this subject.

Your progress report was read with very real interest and a number of comments and questions come to mind.

In administering nicotine to these rabbits you have had the usual problem of translating human dosages into presumed equivalents for small animals. This has always been a problem and it has become something of a convention to make the adjustment on a weight basis. There are some good arguments for using the relative body surface area instead of weight, on the ground that physiological parameters of many kinds are more closely related to surface than to weight. Some of these arguments are reviewed cogently by Finkel in Cancer Research, 18, 853 (1958), (August issue).

The evidences of interaction between cholesterol and nicotine are, of course, the most interesting observations, and one is tempted to begin speculating on possible mechanisms. I recall the hypothesis that hypertension may be a contributing factor in atherosclerosis in the following manner: It is postulated that (1) the inner wall lining of the blood vessels first loses elasticity through degenerative changes influenced perhaps by heredity, aging, malnutrition or other factors, (2) that hypertension contributes toward development of breaks in this lining by purely mechanical effect, especially in zones of maximum tension and, (3) that plaques tend to be initiated by a process

1003537348

Source: https://www.industrydocuments.ucsf.edu/docs/yqll0000

of filtration of suspended material (lipids?) present in the blood stream through the layers of relatively porous material surrounding the inner lining of the vessels.

If this mechanism has any validity one might assume that nicotine would be most likely to affect stage (1) or stage (2). We know little or nothing about stage (1), but it is common pharmacological knowledge that nicotine can slightly and transiently affect blood pressure possibly by stimulating the release of epinephrine from depots.

At any rate, it might be feasible to determine whether hypertensive drugs in general, and epinephrine particularly, would produce the same kind of effect as nicotine when given chronically in small doses along with cholesterol. This might help determine whether the effect of nicotine is in some way specific, or whether it may be explained wholly as a non-specific effect on the prevailing level of blood pressure.

If the mechanism outlined is valid, one would suppose that the role of cholesterol and associated blood lipids was to provide the filterable material for plaque formation once the necessary conditions of vessel-lining fragility and mechanical rupture had been attained.

In this connection I am reminded of a laboratory agency which is interested in the project of developing a fine instrument capable of measuring the elastic strength of blood vessel linings. Do you think that the development of such an instrument would be useful to studies of the kind in which you are engaged?

The stated hypothesis would explain why plaque formation is not extensive when nicotine is given without cholesterol and extra fat although it would not account for the changes you noted in the smaller coronary branch arteries in your nicotine-only group of animals.

Will you by any chance be attending the American Public Health Association in St. Louis October 26-31? I shall be there for two or three days but probably cannot come to Lawrence at this time.

Sincerely yours,

/s/ Robert C. Hockett
Associate Scientific Director

P.S. For reasons suggested by other research projects, I should be much interested in learning whether extra niacin in the diet of these animals would protect them from the synergistic nicotine and cholesterol effect, or whether a niacin deficiency would augment it.

R.C.H.

cc: McKeen Cattell
R.J. Bing -
Julius H. Comroe

1003537349

Source: https://www.industrydocuments.ucsf.edu/docs/yqll0000